REMARKS

The present response does not raise new issues that would require further consideration or search. In particular, Applicants' arguments are based exclusively on evidence that was before the Office when the Office issued the present Office Action. The response further materially reduces or simplifies the issues for appeal, and the response does not enter claims without canceling a corresponding number of finally rejected claims. Accordingly, entry of the response is proper, and Applicants respectfully request reconsideration and reexamination of the present application in light of the following remarks.

1. Status of the Claims

Claims 1-58 are pending. Claims 13-58 are withdrawn. Claims 1-12 stand rejected.

2. Acknowledgement of Information Disclosure Statement

Applicants appreciate consideration of the IDS filed July 11, 2007.

3. Notice of Related Prosecution

The Office asserts that the present application contains subject matter related to several co-pending applications. Prosecution is ongoing in all but one of these applications. The most recent Office Action to issue in the remaining applications as of January 27, 2008, are listed below:

a) Application Serial No. 10/578,522: an Office Action last issued in the '522 application on October 31, 2007. The Office Action cites Ito *et al.*, *Res. Lab. Pharmacol.* Mochida Pharm. Co., Ltd., Tokyo, Japan (1981) in a rejection. The Office cites the '522 application in a rejection for obviousness-type double patenting below.

b) Application Serial No. 10/461,290: an Office Action last issued in the '290 application on December 11, 2007.

c) Application Serial No. 10/727,940: an Office Action last issued in the '940 application on October 2, 2007.

d) Application Serial No. 10/728,286: the '286 application is abandoned.

e) Application Serial No. 10/781,422: an Office Action last issued in the '422 application on September 29, 2007.

f) Application Serial No. 10/827,839: an Office Action last issued in the '839 application on December 28, 2007.

4. Provisional Rejection for Obviousness-Type Double Patenting

Claims 1-12 are provisionally rejected for alleged obviousness-type double patenting over claims 1, 10-14, and 16-20 of co-pending Application Serial No. 10/578,522.

Since the claims at issue are still the subject of ongoing prosecution, Applicants will file a terminal disclaimer as appropriate to obviate the rejection only if proper grounds for double patenting are present when either of the aforementioned applications is allowed. *See* MPEP § 804(I)(B), "Between Copending Applications-Provisional Rejections," 8th ed., revised Sept. 2007. Applicants appreciate the Office's indication that this rejection is held in abeyance.

5. Rejection under 35 U.S.C. § 103

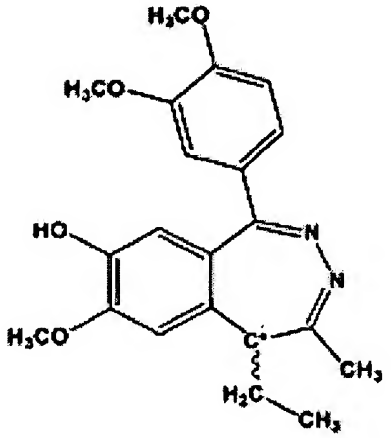
Claims 1-12 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,322,346 ("Kórósi") in view of Ito, *Tokyo Ika Daigaku Zasshi* 39: 269-384 (1981) ("Ito"). Applicants respectfully traverse the rejection.

(A) The legal standard for establishing *prima facie* case obviousness.

Whether a claim is obvious is based on an objective analysis of the scope and content of the prior art, the differences between the prior art and each element of the claimed invention, and the level of skill in the pertinent art. Secondary considerations, such as unexpectedly superior results, may be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *See Graham v. John Deere Co.*, 383 U.S. 1, 15-17 (1966); *see also* M.P.E.P. § 2141. The Federal Circuit recently held: "[The] test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*." *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007). Under this test, the prior art must suggest the specific molecular modifications necessary to achieve the claimed invention. *Takeda*, 83 U.S.P.Q.2d at 1174 (citing cases).

(B) The claimed invention and the teachings of Kórósi and Ito differ in the moieties present at the 7 and 8 position of the 2,3-benzodiazipine ring.

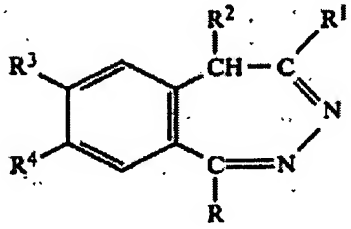
The presently claimed invention is directed to a pharmaceutical composition comprising a 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or a pharmaceutically acceptable salt thereof. The specification discloses that this compound has the following structure (formula I):



I

In formula I, C* is a chiral carbon, and the bond designated ~~~ indicates that the absolute confirmation about the C* may be either (*R*) or (*S*). *See, e.g.*, Specification, page 18, lines 13-16.

Kórósi teaches a compound having the general formula shown below:



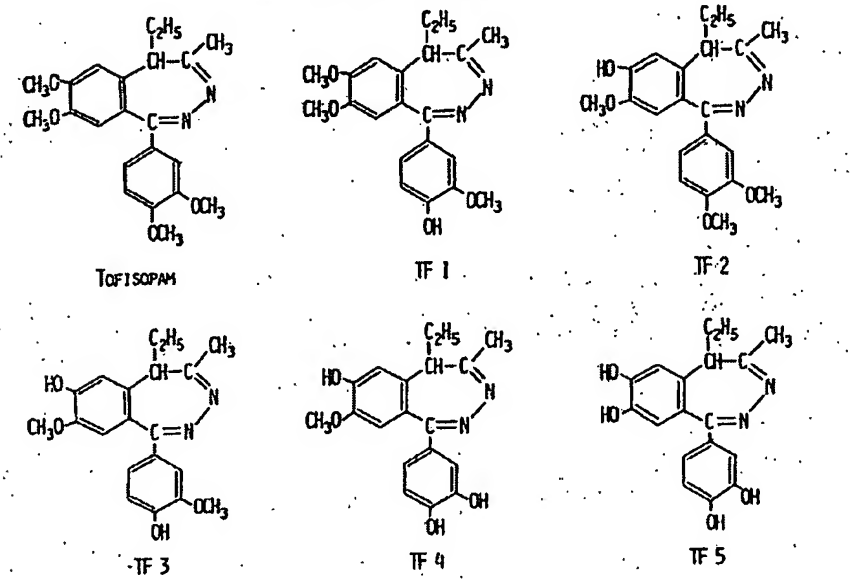
(I)

Kórósi specifically discloses the preparation of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine. Kórósi, col. 8, line 32, *et seq*. Kórósi's compound differs from the claimed compound in two respects:

1) R^3 (i.e., the 7 position) of Kórósi is a hydroxyl group, whereas the claimed compound has a methoxy group at the 7 position; and
2) R^4 (i.e., the 8 position) of Kórósi is a methoxy group, whereas the claimed compound has a hydroxyl group at the 8 position.

Ito discloses tofisopam ("TF") and five related derivatives; one derivative, TF 2, is structurally identical to Kórósi's exemplified compound. *See* Ito, Figure 4:

Fig.-1 Chemical structures of tofisopam and related compounds



Ito measures several pharmacological activities of these derivatives. *See* Ito, Table 10:

Table 10 Various pharmacological effects of tofisopam and related compounds

Compound	Inhibition of aggression (%)	Inhibition of muricide (%)	Anti-noradrenergic activity	
			pA_2	pD'_2
Control	0.0(7)	0.0(5)	—	—
Tofisopam	50.0(8)	40.0(5)	4.09±0.04	3.86±0.07
TF 1	0.0(5)	0.0(5)	4.57±0.14	4.01±0.12
TF 2	0.0(5)	20.0(5)	No effect	No effect
TF 3	28.6(7)	20.0(5)	3.36±0.15	3.46±0.18
TF 4	20.0(5)	0.0(5)	No effect	No effect
TF 5	0.0(5)	0.0(5)	No effect	No effect

In in vivo test, 100 mg/kg of all compounds were administered orally. Aggression is induced by isolation mice in small cages for 4 weeks. Muricide reaction is observed in olfactory bulbectomized rats. Anti-noradrenergic activity is tested in isolated rat vas deferens. No. in parentheses is No. of animals used. See explanation in Table 3.

Inspection of Table 10 indicates that TF 1 alone showed statistically the same anti-noradrenergic (anti-NAD) activity as tofisopam. ***All*** the other tested activities of ***all*** the other tofisopam derivatives were undetectable or lower than tofisopam. When the various derivatives were administered in an amount 40 times higher that used in Table 10, all the derivatives demonstrated a lower acute toxicity than tofisopam. *See* Ito, page 18.

Ito, a skilled artisan in the relevant art, interprets the toxicity results as follows (page 23, fifth paragraph):

> The mortality rate in oral administration of 4,000 mg/kg TF was 60%, while no cases of mortality were found in oral administration of 4,000 mg/kg TF 1, TF 2, TF 3, TF 4, or TF 5. These results suggest that the methoxy groups in the 7 and 8 positions of the 2,3-benzodiazepine ring, and the methoxy groups in the 3 and 4 positions of the benzene ring have no effect on the acute toxicity of the drug.

As shown in Table 10, TF 1 alone shows the same anti-NAD activity as tofisopam. In TF 2 through TF 5, the methoxy group at the 7 position is substituted with a hydroxyl group. Ito states (paragraph bridging pages 23-24):

> We studied the pA_2 value[1] in relation to NAD using rats' isolated ductus deferens and found that the values were 4.09 ± 0.04 for TF 1 and 3.36 ± 0.15 for TF 3, indicating that TF 1 had a similar effect to that of TF. These results suggest that in the anti-NAD effect of TF, the role of the methoxy group at the 4 position of the benzene ring is small, while the methoxy group at the 7 position of the 2,3-benzodiazepine rings plays the most important role.

Thus, Ito suggests that the 7 position methoxy group "plays the most important role" in the anti-NAD effect of tofisopam.

(C) The Office does not establish a proper *prima facie* case of obviousness, because it fails to consider the prior art as a whole, particularly those teachings of Ito that lead away from the claimed invention.

To make a *prima facie* case of obviousness, the Office must provide reasons or suggestion in the prior art to make the specific molecular modifications necessary to achieve the claimed invention. *Takeda*, 83 U.S.P.Q.2d at 1174. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983).

In the present case, the Office alleges that the claimed compound would have been obvious because it was disclosed in the cited art. Office Action, page 8. The general formula I of Kórósi, however, encompasses a genus containing perhaps millions of compounds. The R moiety of Kórósi alone encompasses all heterocyclic groups containing one or two nitrogen, oxygen, or sulfur atoms. The claimed compound is not among the

species of this large genus disclosed in Kórósi. Combined with the disclosure of Ito, the cited art in fact indicates a preference ***leading away*** from the claimed compound, for the reasons set forth below. *See, e.g.*, *In re Baird*, 16 F.3d 380, 383, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

In this regard, the Office alleges that the artisan of ordinary skill would have made two modifications to the compound disclosed in Kórósi based on the teachings of Ito: (1) a substitution of the 7 hydroxyl group with a methoxy group and (2) a substitution of the 8 methoxy group with a hydroxyl group. The Office alleges that Ito suggests the first substitution because the methoxy group at the 7 position "plays an important role." The Office alleges that Ito suggests the second substitution because substituting the 8 position methoxy group with a hydroxyl group decreases toxicity.

Ito suggests neither substitution. To the contrary, Ito's results suggest that a substitution of the methoxy group at position 7 with a hydroxyl group is deleterious: ***all*** tofisopam derivatives with this substitution, i.e., all the derivatives except TF 1, show lower or undetectable activity than tofisopam or TF 1 in ***every*** test. *See* Ito, Table 10. Ito suggests that a methoxy group at position 7 "plays an important role," because TF 1 was the only tofisopam derivative to exhibit anti-NAD activity. *See* Ito, pages 23-24. Accordingly, Ito ***teaches away*** from substituting the methoxy group at position 7 with a hydroxyl group to avoid the disadvantage of lower anti-NAD activity.

Ito teaches two tofisopam derivatives that differ only at the 8 position, TF 4 and TF 5. Ito teaches, however, that "no cases of mortality were seen in administration of 4,000 mg/kg . . . TF 4 and TF 5." Ito, page 18. In other words, Ito suggests no advantage or disadvantage with a methoxy group (TF 4) or a hydroxyl group (TF 5) at the 8 position. Ito reports that "methoxy groups in the 7 and 8 positions of the 2,3-benzodiazepine ring, . . . have ***no effect*** on the acute toxicity of TF." Ito, page 23 (emphasis added).

For these reasons, the Office has not provided the requisite reasons or suggestion in the prior art to make the specific molecular modifications necessary to achieve the claimed invention. In particular, the Office has not demonstrated from the record that Ito suggests modifying Kórósi to achieve the claimed invention. *See Takeda*, 83 U.S.P.Q.2d at 1174. The Office further has ignored disclosure in Ito that teaches away from the proposed

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[1] Ito states that the pA_2 value measures the degree of competitive antagonism of a compound, whereas

modification of the 7 position. *See Gore & Assoc.*, 721 F.2d at 1550. Accordingly, the Office has not made a *prima facie* case of obviousness, and the rejection should be withdrawn.

The Office contends that a comparison between TF 1 and TF 2 is not a "true comparison" because the derivatives have different substituents on different ring moieties. Office Action, page 13. Ito, a skilled artisan, draws his conclusions based precisely on a comparison of TF, TF 1, TF 2, TF 3, TF 4, and TF 5, as set forth above. Thus, the level of skill in the relevant art is sufficiently high for the artisan to compare the properties of tofisopam derivatives with substitutions on different ring moieties.

(D) The specification evidences that the claimed compound has unexpectedly superior properties compared to the compound of Kórósi.

It is well established that evidence of unobvious or unexpected properties in a claimed compound may rebut a *prima facie* case of obviousness. *See, e.g., In re Papesch*, 137 USPQ 43, 48 (C.C.P.A. 1963). It is equally well established that a compound need not be better in all respects than prior art compounds used for the same purposes. It may be better in some respects, worse in others. *Deutsche Gold-und Silber-Scheideanstalt Vormals Roessler v. Comm'r Patents*, 148 U.S.P.Q. 323, 325 (D.D.C. 1966); *In re Chupp*, 2 U.S.P.Q.2d 1437, 1440 (Fed. Cir. 1987) (new compound patentable based on unexpected results in one of a spectrum of common properties); *see also* MPEP § 706.02(a)(II). A showing of unexpected results must provide a comparison with the closest prior art. *See In re Harris*, 74 U.S.P.Q.2d 1951, 1955 (Fed. Cir. 2005).

In the present case, rebuttal evidence is unnecessary, because the Office has not made a proper *prima facie* case of obviousness. Nevertheless, solely to expedite prosecution, Applicants emphasize evidence in the specification that the claimed compound has unexpectedly superior properties, compared to the compound disclosed in Kórósi and the TF 2 compound disclosed in Ito. The Office considers this compound to be the closest prior art compound. *See Harris*, 74 U.S.P.Q.2d at 1955. It should be noted in this context that the specification also discloses unexpectedly superior results with respect to two other TF derivatives disclosed in Ito, TF 1 and TF 3.

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the pD'_2 value is an expression of non-competitive antagonism. Ito, page 20, second paragraph.

The specification demonstrates the usefulness of the claimed compound in the treatment of disorders mediated by adenosine, TXA_2, and LTB_4. *See, e.g.*, Specification, Examples 3-5, page 44, *et seq*. Table 2 discloses a side-by-side comparison of the claimed compound with the closest prior art, i.e., the compound disclosed in Kórósi and Ito (TF 2), as well as two other TF derivatives disclosed in Ito, TF 1 and TF 3:

Compound Name	TXA2 % inhibition @ 10μM	LTB_4 % inhibition @ 10μM	Adenosine nonselective @10μM
1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **[claimed]**	48.26	35.96	61.50
1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **[TF 1]**	1.98	49.89	inactive
1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine **[Kórósi; TF 2]**	42.69	20.35	6.73
1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine **[TF 3]**	44.02	inactive	22.40

As is evident from Table 2, the claimed compound shows superior activity to the compound of Kórósi in all activities tested. In particular, the activity of the claimed compound is over ***9-fold higher*** in an assay that measures the inhibition of the binding of labeled NECA to the adenosine receptor. *See, e.g.*, Specification, page 46, line 14, *et seq*. This result suggests that the claimed compound is unexpectedly more effective than the compound of Kórósi in treating diseases mediated by adenosine. Unexpectedly superior results in one property, if not all properties, of a compound is sufficient to rebut a case of *prima facie* obviousness. *See Deutsche Gold*, 148 U.S.P.Q. at 325; *Chupp*, 2 U.S.P.Q.2d at 1440. The results in the specification further demonstrate that the claimed compound demonstrates unexpectedly superior TXA2 inhibition and inhibition of the binding of labeled NECA to the adenosine receptor, compared to TF 1 of Ito. Finally, the specification demonstrates that the claimed compound possesses unexpectedly superior LTB_4 inhibition, compared to TF 3 of Ito. For all these reasons, even if the Office *arguendo* were to establish

a proper *prima facie* case of obviousness, the present evidence of unexpectedly superior properties of the claimed compound would rebut such a determination.

As a final matter, the Office asserts that the date of the *Norris* decision is irrelevant, because *Norris* requires to Office consider the factual circumstances surrounding the patented subject matter. Office Action, pages 11-12. The Office certainly would agree, though, that *Norris* is overruled to whatever extent it conflicts with later binding precedent, e.g. *Graham*. In any event, an objective consideration of the facts relevant to obviousness, required not only by *Norris* but also by *Graham*, compels the conclusion that the claimed invention is not obvious, for all the reasons set forth above. The statement that the determination of obviousness must be based on an objective fact-based inquiry cannot trump the *conclusion*, made in view of the same fact-based inquiry, that the present claims are patentable. In other words, the Office cannot announce a *per se* rule in this application based merely on the statement of the legal standard for determining obviousness in *Norris*.

(E) The Office's allegations regarding the (R) and (S) forms of the claimed compound do not establish a *prima facie* case of obviousness.

The remaining remarks in the Office Action address the alleged obviousness of the (*R*) and (*S*) forms of the claimed compound, which are recited in dependent claims. Because the Office has not made a *prima facie* case of obviousness against claim 1, it cannot use these arguments to allege *prima facie* obviousness of claims depending on claim 1. Applicants, in any event, respectfully but categorically traverse this aspect of the rejection, for all the reasons set forth in their Reply filed July 9, 2007, incorporated by reference herein.

For all these reasons, the rejection of claims 1-12 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

CONCLUSION

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience. If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573.

Respectfully submitted

By: _____

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